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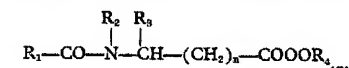
(54) DERMATOLOGICAL COMPOSITIONS

(71) We, DR. KARL THOMAE G.M.B.H., a German Body Corporate, of Biberach an der Riss, Federal Republic of Germany, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to compositions comprising acylamino-carboxylic acid derivatives as active ingredient.

In the literature many acylamino-carboxylic acid derivatives are described (see for example C.A. 66, 29058 (1967)). No biological activity has however hitherto been described for these compounds.

The present invention is based upon the discovery that compounds of general formula



(I)

[wherein R_2 represents a hydrogen atom or an alkyl group with 1 to 3 carbon atoms; R_3 represents a hydrogen atom, an alkyl group with 1 to 6 carbon atoms optionally substituted by a methylthio group or a benzyl group; n represents the number 0, 1 or 2; and either R_1 represents a hydrogen atom, a trifluoromethyl group or an alkyl group with 1 to 4 carbon atoms and R_4 represents a straight- or branched-chain alkyl group with 8 to 24 carbon atoms; or R_1 represents a straight- or branched chain alkyl group with 17 to 24 carbon atoms, a phenyl group optionally substituted by an alkyl group, a halogen atom or a nitro group, or a biphenylyl group and R_4 represents a hydrogen atom or a straight- or branched-chain alkyl group with 1 to 4 carbon atoms] show valuable therapeutic and cosmetic properties, especially for treatment and care of the skin.

Thus according to one feature of the present invention there is provided a composition for the treatment of the skin which comprises at least one compound of formula I as hereinbefore defined in association with a carrier or excipient as herein defined. The expression "carrier or excipient" is used herein to designate carriers or excipients suitable for use in the formulation of compositions for topical application in the treatment of the skin, but is not to be interpreted as including common solvents alone e.g. ethanol, non-sterile water, which together with the compounds of general formula I give rise to mere simple solutions, suspensions or dispersions.

The new compositions according to the invention may, for example, conveniently take the form of ointments, creams, aerosols, powders, tinctures, gels, pastes, essences or lotions. Appropriate carriers and excipients used in the formulation of creams for topical application according to the invention are, for example, waxes, self-emulsifying waxes, creaming and dispersing agents. Lotions generally contain these same excipients in addition to non-ionic surface active agents and paraffin oil. Ointments may comprise a compound of formula I as hereinbefore defined in association with an ointment base of, for example, wool grease, paraffin oil, petroleum jelly and a suitable dispersing agent. Suitable excipients used in the preparation of gels according to the invention include thickening, suspending, dispersing, emulsifying and gelling agents. Aerosol sprays may be of a foam or dry spray type and in general they contain a propellant and a non-ionic surface-active agent which may be water or oil-dispersible. Foam aerosols additionally contain a creaming or foaming agent. Powder compositions conveniently comprise the active ingredient intimately dispersed in a dusting powder mixture of, for example, magnesium stearate, maize starch and finely-divided silicon dioxide. Pastes according to the invention generally contain a swelling agent dispersed in aqueous solution, the active ingredient(s) and a dispersing agent therefor. All the forms of administration may additionally contain, if desired, mild antiseptics e.g. isopropanol, preservatives, pigment and colour-

ing matter and perfume oils.

The concentration of the compound(s) of formula I in the composition is in general conveniently from 0.1 to 20%, and preferably from 0.25 to 5%, by weight. The composition may, if desired, additionally contain other active ingredients, e.g. vitamins, corticosteroids, steroids, antihistamines, keratolytics, antibiotics or disinfectants.

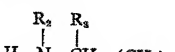
As already above mentioned, the compositions according to the invention have interesting therapeutic and cosmetic properties for treatment and care of the skin. In particular they in general possess one or more activities selected from the following:— sebaceous inhibitory, antiphlogistic, antiproliferative, antidandruff, capillary stabilising, local anaesthetic, skin conditioning, skin protecting and skin moisturising activities. One or more of the activities may predominate according to the structure of the compounds.

Thus according to a further feature of the present invention there is provided a method of conditioning, protecting and/or moisturising the skin which comprises applying a composition according to the invention as hereinbefore defined to the skin.

Preferred compositions according to the invention by virtue of their particularly favourable cosmetic and therapeutic properties are those wherein the active ingredient is a compound of formula I wherein R_2, R_3 and n are as hereinbefore defined, R_1 represents a hydrogen atom, a trifluoromethyl group or an alkyl group with 1 to 4 carbon atoms and R_4 represents a straight- or branched-chain alkyl group with 8 to 24 carbon atoms.

The compounds of general formula I, which are partially known from the litreature, may be prepared according to the following process:

Acylation of a compound of formula



(II)

(wherein R_2 to R_4 and n are defined as above) with a reactive derivative of an acid of formula

$$R_1—COOH \qquad (III)$$

(wherein R_1 is defined as above).

The reaction is advantageously carried out with the anhydride or acid halide of the acid of formula III, conveniently in the presence of a solvent such as water and preferably in the presence of a base such as sodium hydroxide or pyridine. The reaction is preferably effected at temperatures of from 0 to 100°C.

The therapeutic and cosmetic activities of the compound of general formula I may be tested according to the following methods:

1. *Determination of the influence on skin oiling* by the glass block method (see Schaefer and Kuhn-Bussius, Arch. Klin. exper. Derm. *238*, 429 to 435 (1970)):

Roughened glass blocks are pressed onto the skin samples to be tested. The skin oil present renders the glass blocks more transparent. Subsequently, the transmittance of the glass blocks is measured using a photometer. Before the measurement of the re-oiling of the skin, the skin fat present is taken up with plastic foil.

In tests which have been carried out, 0.25 ml of a 5% alcoholic solution of one of the substances under investigation was applied to one side of the forehead of 5 to 10 test persons. 0.25 ml of alcohol was applied to the other side which served as the control. After 1½ hours the skin fat present was removed with plastic foil and after a further 3 hours the extent of re-oiling was determined.

The percentage rise in the transparency of the imprinted blocks is proportional to quantity of skin oil present:

Substance	Mean extinction values Control	Treatment	Difference
N-Acetyl-glycine hexadecyl ester	66.0	75.5	9.5
N-Acetyl-alanine hexadecyl ester	66.5	74.0	7.5
N-Acetyl-sarcosine hexadecyl ester	77.5	86.5	9.0

2. *Determination of the antiphlogistic activity* against dinitrochlorobenzene eczema (see A. I. Scott, Brit. J. Dermatol. *77*, 586 (1965)).

A 5% alcoholic solution of the substance under investigation was applied to the shaved flanks of each of 10 guinea pigs sensitised with dinitrochlorobenzene. The shaved flanks of the

control animals were treated with pure alcohol. The treatment took place 1/2 hours before initiating an allergic reaction with a 0.1% solution of dinitrochlorobenzene in acetone. Visual observation of the results took place after 22 hours.

Substance	Percentage restraint of the dinitrochlorobenzene eczema (as compared with the controls)
N-Formyl-glycine hexadecyl ester	50
N-Acetyl-glycine hexadecyl ester	46
N-Propionyl-glycine hexadecyl ester	34
N-Acetyl-β-alanine hexadecyl ester	30
N-Acetyl-sarcosine hexadecyl ester	20
N-Acetyl-alanine hexadecyl ester	19
N-Octadecanoyl-glycine	36
N 4'-Phenylbenzoyl-4-aminobutyric acid	35

Furthermore the compounds of general formula I are practically non-toxic.

The following examples serve to illustrate the preparation of compositions according to the invention:

Preparation A.

N-Acetyl-glycine octadecyl ester

3.0 g of glycine ethyl ester hydrochloride and 15.0 g of octadecanol were heated up to 100°C and hydrogen chloride was introduced for 3 hours at this temperature. After cooling, the solidified melt was suspended in 500 ml of ether and the solid residue of the glycine octadecyl ester hydrochloride was suction filtered. The crude ester hydrochloride was suspended in water and converted into the base by the addition of an excess of sodium hydrogen carbonate with stirring. The ester was suction filtered, dried, added to 50 ml of acetic anhydride and heated for one hour on the water bath. Subsequently the solution was poured into 1 l of water and the precipitate was suction filtered and dried. The crude product was purified by crystallization three times from petroleum ether. Yield: 2.1 g (26% of theory), m.p.: 78 to 79°C.

Preparation B.

N-Octadecanoyl-glycine

7.5 g (0.1 mol) of glycine was dissolved in a solution of 4.0 g (0.1 mol) of sodium hydroxide in 150 ml of water. 30 g (0.1 mol) of octadecanoyl chloride were added and the mixture was shaken until N-octadecanoyl-glycine crystallized out. Subsequently, the mixture was acidified with concentrated hydrochloric acid. The precipitate was suction filtered and washed with water. After drying, the solid product was recrystallized twice from ethyl acetate.

Yield: 25 g (73% of theory), m.p.: 120°C

The following compounds were prepared analogously to Preparations A and B (see for example Rec. trav. chim. *77*, 267 (1958) or J. Am. Chem. Soc. *78*, 172 (1956)):

N-Acetyl-leucine hexadecyl ester
M.p.: 37 to 38°C

N-Acetyl-methionine hexadecyl ester
M.p.: 59 to 60°C

N-Acetyl-phenylalanine hexadecyl ester
M.p.: 75 to 76°C

N-Acetyl-sarcosine hexadecyl ester
M.p.: 58 to 59°C

N-Formyl-glycine hexadecyl ester
M.p.: 64 to 65°C

N-Propionyl-glycine hexadecyl ester
M.p.: 67 to 68°C

N-Trifluoroacetyl-glycine hexadecyl ester
M.p.: 68 to 70°C

N-Acetyl-β-alanine hexadecyl ester
M.p.: 65 to 66°C

N-Acetyl-glycine dodecyl ester
M.p.: 59 to 60°C

N-Acetyl-glycine tridecyl ester
M.p.: 65 to 66°C

N-Acetyl-glycine tetradecyl ester
M.p.: 69 to 70°C

N-Acetyl-glycine pentadecyl ester
M.p.: 73 to 74°C

N-Acetyl-glycine hexadecyl ester
M.p.: 74 to 75°C

N-Acetyl-glycine heptadecyl ester
M.p.: 76 to 77°C

N-Acetyl-glycine octadecyl ester
M.p.: 78 to 79°C

N-Acetyl-glycine nonadecyl ester
M.p.: 79 to 80°C

N-Acetyl-glycine eicosyl ester
M.p.: 83 to 84°C

N-Acetyl-glycine docosyl ester
M.p.: 86 to 87°C

N-Acetyl-alanine hexadecyl ester
M.p.: 64 to 65°C

N-Acetyl-alanine octadecyl ester
M.p.: 70 to 71°C

N-Acetyl-β-alanine eicosyl ester
M.p.: 76°C

N-Acetyl-β-alanine dodecyl ester
M.p.: 50°C

N-Acetyl-4-aminobutyric acid tetradecyl ester
M.p.: 58°C

N-Acetyl-4-aminobutyric acid octadecyl ester
M.p.: 71°C

N-Benzoyl-4-aminobutyric acid octadecyl ester
M.p.: 76°C

N-Octadecanoyl-glycine
M.p.: 120°C

N-Docosanoyl-glycine
M.p.: 121°C

N-Octadecanoyl-alanine
M.p.: 109°C

N-Octadecanoyl-valine
M.p.: 93°C

N-Octadecanoyl-leucine
M.p.: 96°C

N-Docosanoyl-leucine
M.p.: 98°C

N-Benzoyl-β-alanine
M.p.: 103 to 105°C

N-4-Phenylbenzoyl-β-alanine
M.p.: 103 to 105°C

N-Octadecanoyl-4-amino-butyric acid
M.p.: 100 to 102°C

N-Benzoyl-4-amino-butyric acid
M.p.: 88 to 89°C

N-4'-Phenylbenzoyl-4-amino-butyric acid
M.p.: 181°C

N-Octadecanoyl-sarcosine
M.p.: 71 to 72°C

N-Octadecanoyl-glycine methyl ester
M.p.: 83 to 84°C

N-Octadecanoyl-glycine ethyl ester
M.p.: 82 to 83°C

N-Octadecanoyl-alanine methyl ester
M.p.: 76 to 77°C

N-Octadecanoyl-phenylalanine isopropyl ester
M.p.: 69 to 70°C

Example 1.

Cream with N-acetyl-glycine hexadecyl ester

Composition:

N-Acetyl-glycine hexadecyl ester	3.0 g
Benzalkonium chloride	0.1 g
Cremophor O	4.0 g
Glycerine monostearate	4.0 g
"Lanette" O (registered Trade Mark)	5.0 g
Walrat	3.0 g
"Cetiol" V (registered Trade Mark)	10.0 g
Distilled water ad	100.0 ml

Method of preparation:

Benzalkonium chloride was dissolved in warm water at 70°C (I). The active ingredient was suspended in a mixture of molten (70°C) Cremophor O, glycerine monostearate, "Lanette" O, Walrat and "Cetiol" V (II). II was subsequently emulsified in I at 70°C and finally cooled whilst stirring.

Example 2.

Cream with N-octadecanoyl-glycine

Composition:

N-Octadecanoyl-glycine	1.0 g
Benzalkonium chloride	0.1 g
Cremophor O	4.0 g
Glycerine monostearate	4.0 g
"Lanette" O	5.0 g
Walrat	3.0 g
"Cetiol" V	10.0 g
Distilled water ad	100.0 ml

Preparation analogous to Example 1.

Example 3.

Gel with N-acetyl-glycine hexadecyl ester

Composition:

N-Acetyl-glycine hexadecyl ester	3.0 g
"Carbopol" 940 (registered Trade Mark)	0.6 g
Triethanolamine	0.6 g
Cremophor EL	5.0 g
Isopropanol	30.0 g
Distilled water ad	100.0 ml

Method of preparation:

A solution of the active ingredient, Cremophor EL and triethanolamine in isopropanol was mixed with an aqueous solution of "Carbopol".

Example 4.

Bath essence with N-acetyl-glycine hexadecyl ester

Composition:

N-Acetyl-glycine hexadecyl ester	5.0 g
"Texapon" N 25 (registered Trade Mark)	30.0 g
"Comperlan" OD (registered Trade Mark)	5.0 g
Isopropanol	20.0 g
Ethereal oil	2.0 g
Distilled water ad	100.0 ml

Method of preparation:

A solution of the active ingredient and the ethereal oil in isopropanol was stirred with an aqueous solution of "Texapon" N 25 and "Comperlan" OD.

Example 5.

Dry-spray with N-acetyl-glycine hexadecyl ester

Composition:

N-Acetyl-glycine hexadecyl ester	3.0 g
"Span" 85 (registered Trade Mark)	0.4 g
Propellant 11 A	3.0 g
Propellant 12/114 40:60	93.6 g

Method of preparation:

The active ingredient, "Span" 85 and Propellant 11 A were mixed in a ball mill. The mixture obtained (cooled to −15°C) was added to the propellant mixture, which itself was cooled to −40°C to −50°C with stirring.

Example 6.

Lotion with N-octadecanoyl-glycine

Composition:

N-Octadecanoyl-glycine	3.0 g
"Span" 40	3.0 g
Cremophor O	2.0 g
"Lanette" O	2.0 g
Walrat	1.0 g
"Cetiol" V	5.0 g
Paraffin oil subl.	1.0 g
"Nipagin" M (registered Trade Mark)	0.1 g
Distilled water ad	100.0 g

Method of preparation:

"Span" 40, Cremophor O, "Lanette" O, Walrat, "Cetiol" V and paraffin oil were melted at 70°C, and the active ingredient dissolved therein. The "Nipagin" was dissolved in distilled water which was heated up to 80°C. The fat melt was added to the solution cooled to 70°C and the mixture was subsequently homogenised and cooled with stirring.

Example 7.

Shampoo with N-acetyl-glycine hexadecyl ester

Composition:

N-Acetyl-glycine hexadecyl ester	3.0 g
Zetasol SE 35 T	55.0 g
"Tylose" MH 300 (registered Trade Mark)	1.0 g
"Nipagin" M	0.5 g
Distilled water ad	100.0 g

Method of preparation:

The distilled water was heated to 80°C, the "Nipagin" M was dissolved therein and the "Tylose" was suspended in the solution. The active ingredient was distributed in a mixture of Zetasol and perfume oil with a high speed stirrer and the "Tylose" slurry was added. The suspension was finally homogenised and deaerated.

Example 8.

Powder with N-acetyl-glycine hexadecyl ester

Composition:

N-Acetyl-glycine hexadecyl ester	3.0 g
"Aerosil" (registered Trade Mark)	1.0 g
Magnesium stearate	0.2 g
ANM Maize starch ad	100 0 g

Method of preparation:

The active ingredient, "Aerosil" and magnesium stearate was added to one third of the maize starch and mixed intimately. Subsequently, the residual maize starch was added to the mixture and mixed intimately.

Example 9.

Paste with N-(4'-phenylbenzoyl)-4-amino-butyric acid

Composition:

N-(4'-Phenylbenzoyl)-4-amino-butyric acid	3.0 g
Lanogen 1500	20.0 g
Isopropanol	45.0 g
Veegum-pharm.	10.0 g
Pigment and colouring matter	1.0 g
Perfume oil	0.2 g
Distilled water ad	100.0 ml

Method of preparation:

The active ingredient was dissolved in Lanogen at 60°C (I). The perfume oil was dissolved in isopropanol (II). The distilled water was heated up to 60°C and the Veegum was added and left to swell. Solutions I and II were added and mixed intimately with the Veegum and the mixture was finally homogenised.

Example 10.

Gel with N-acetyl-glycine hexadecyl ester together with an antibiotic

Composition:

N-Acetyl-glycine hexadecyl ester	3.0 g
Chloroamphenicol	0.1 g
Salicylic acid	0.5 g
Isopropanol	25.0 g
"Bentone" EW (registered Trade Mark)	2.0 g
Triethanolamine	1.8 g
Distilled water ad	100.0 ml

Method of preparation:

Analogously to Example 3.

Example 11.

Gel with N-acetyl-glycine hexadecyl ester together with an antibiotic

Composition:

N-Acetyl-glycine hexadecyl ester	3.0 g
Tetracyclin hydrochloride	0.1 g
Salicylic acid	0.5 g
"Bentone" EW	2.0 g
Triethanolamine	1.8 g
Distilled water ad	100.0 g

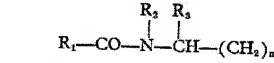
Method of preparation:

Analogously to Example 3.

Analogous compositions may be prepared using other compounds of formula I.

WHAT WE CLAIM IS:—

1. A composition for treatment of the skin which comprises as active ingredient at least one compound of formula



I

[wherein R_2 represents a hydrogen atom or an alkyl group with 1 to 3 carbon atoms; R_3 represents a hydrogen atom, an alkyl group with 1 to 6 carbon atoms optionally substituted by a methylthio group or a benzyl group; n represents the number 0, 1 or 2; and either R_1 represents a hydrogen atom, a trifluoromethyl group or an alkyl group with 1 to 4 carbon atoms and R_4 represents a straight- or branched-chain alkyl group with 8 to 24 carbon atoms; or R_1 represents a straight- or branched chain alkyl group with 17 to 24 carbon atoms, a phenyl group optionally substituted by an alkyl group, a halogen atom or a nitro group, or a biphenylyl group and R_4 represents a hydrogen atom or a straight- or branched-chain alkyl group with 1 to 4 carbon atoms] in association with a carrier or excipient (as herein defined).

2. A composition as claimed in claim 1 wherein the said active ingredient is a compound of formula I wherein R_2, R_3 and n are as defined in claim 1, R_1 represents a hydrogen atom, a trifluoromethyl group or an alkyl group with 1 to 4 carbon atoms and R_4 represents a straight- or branched-chain alkyl group with 8 to 24 carbon atoms.

3. A composition as claimed in claim 1 or 2 wherein the concentration of the compound(s) of formula I is from 0.1 to 20% by weight.

4. A composition as claimed in claim 3 wherein the concentration of the compound(s) of formula I is from 0.25 to 5% by weight.

5. A composition as claimed in any of the preceding claims which additionally contains at least one further active ingredient, selected from vitamins, corticosteroids, steroids, antihistamines, keratolytics, antibiotics, and disinfectants.

6. A composition as claimed in any of the preceding claims in the form of an ointment, cream, aerosol, powder, tincture, gel, paste, essence or lotion.

7. A composition according to claim 1 or claim 2 substantially as herein described.

8. A composition substantially as herein described in any of Examples 1 to 11.

9. A cream for the treatment of the skin comprising a compound of formula I as defined in claim 1 in association with an appropriate carrier or excipient.

10. An ointment for the treatment of the skin comprising a compound of formula I as defined in claim 1 in association with an appropriate carrier or excipient.

11. A gel for the treatment of the skin comprising a compound of formula I as defined in claim 1 in association with an appropriate carrier or excipient.

12. An aerosol for the treatment of the skin comprising a compound of formula I as defined in claim 1 in association with an appropriate carrier or excipient.

13. A powder for the treatment of the skin comprising a compound of formula I as defined in claim 1 in association with an appropriate carrier or excipient.

14. A tincture for the treatment of the skin which contains a compound of formula I as defined in claim 1.

15. A paste for the treatment of the skin comprising a compound of formula I as defined in claim 1 in association with an appropriate carrier or excipient.

16. An essence for the treatment of the skin which contains a compound of formula I as defined in claim 1.

17. A lotion for the treatment of the skin comprising a compound of formula I as defined in claim 1 in association with an appropriate carrier or excipient.

18. A shampoo for the treatment of the skin comprising a compound of formula I as defined in claim 1 in association with an appropriate carrier or excipient.

19. A dry spray for the treatment of the skin comprising a compound of formula I as defined in claim 1 in association with an appropriate carrier or excipient.

20. A composition as claimed in any of claims 9 to 19 wherein the concentration of the compound of formula I is from 0.1 to 20% by weight.

21. A composition as claimed in claim 20 wherein the concentration of the compound of formula I is from 0.25 to 5% by weight.

22. A composition as claimed in any of claims 9 to 21 which additionally contains at least one further active ingredient, selected from vitamins, corticosteroids, steroids, antihistamines, keratolytics, antibiotics and disinfectants.

23. A method of conditioning, protecting and/or moisturising the skin which comprises applying thereto a composition as claimed in any of claims 1 to 8.

24. A method of conditioning, protecting and/or moisturising the skin which comprises applying thereto a composition as claimed in any of claims 9 to 22.

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